REMARKS/ARGUMENTS

Claims 1-22, 25-28, 30-32 and 34 are pending.

Claims 23, 24,29 and 33 have been canceled.

Claims 1-22,25 and 26 have been withdrawn.

Claims 27,28,30-32 and claim 34, only as drawn to the species cytotoxic moieties, are currently under consideration.

In view of the examiner's earlier restriction requirement, applicant retains the right to present claims 1-22,25 and 26 in a divisional application.

In response to the Office Action of August 7, 2006, Applicant requests re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Objections:

Deposit information drawn to antibody H460-22-1 is objected to because the deposit was made after the effective filing date of the application and no corroborative statement for antibody H460-22-1 and the hybridomas cell line deposited with the ATCC as Accession Number PTA-4622, see CFR 1.804(b) was submitted.

The specification is objected to for not specifying the depository in which PTA-4622 was deposited in the amendment of February 6, 2004, see CFR 1.803.

Accordingly, it is respectfully submitted that the above-noted objections have been cured by submission herewith of a

Corroboration Statement by David S.F. Young, President and CSO of the Assignee, Arius Research, Inc., and amendment of the specification to include reference to the deposit having been made with the American Type Culture Collection, in Manassas, Virginia.

Rejections under 35 USC 112:

Claims 29, 33, and 34 stand rejected as being indefinite because claims 29 and 33 recite the phrase "chimerized antibody". The exact meaning of the word chimera is not known. The term chimera is generic to a class of antibodies, which are products of genetic shuffling of antibody domains and other active proteins. The term encompasses antibodies fused to non-immunoglobulin proteins as well as antibodies wherein any domain of the antibody is substituted by corresponding regions or residues of human antibodies including but not limited to CDR grafted antibodies. Thus the metes and bounds of the claim protection sought cannot be determined.

Claims 29, 33, and 34 further stand rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. Claims 29, 33, and 34, which are broadly drawn to a chimerized monoclonal antibody produced by the hybridomas deposited with ATCC as Accession Number PTA-4622 have no clear support in the specification and the claims as

originally filed. Although applicant states that claims of this format are preferred in applications with similar scope, applicant is reminded that claim limitations require support in the specification as originally filed. A review did not reveal the term chimerized in either the specification or claims as originally filed. Thus, the subject matter claimed in claims 29, 33, and 34 broadens the scope of the invention as originally disclosed in the specification.

Accordingly, claims 29 and 33 have been cancelled; and reference to those claims in claim 34 has likewise been removed.

Claims 27-34 further stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody that binds specifically to NCI-460 cells, does not reasonably provide enablement for an isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as Accession Number PTA-4622, an isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as Accession Number PTA-4622 which is humanized, chimerized, and conjugated to cytotoxic moieties. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Examiner states the following:

> The claims are broadly drawn to an isolated

monoclonal antibody produced by the hybridoma deposited with the ATCC as Accession Number PTA-4622 and various forms of this monoclonal antibody.

The specification teaches that the invention relates to the production of anti-cancer, antibodies customized for the individual patient which may be combined with chemotherapeutic agents that can be used for therapeutic and diagnostic purposes, p. 1, lines 9-12. Furthermore, the specification teaches that each individual who presents with cancer is unique and has a cancer that is as different from other cancers as that person's identity, p. 1, lines 16-18.

The specification teaches that the antibodies of the invention have either cell-killing (cytotoxic) or cell-growth inhibiting (cytostatic) properties. They can be used in aid of staging and diagnosis of cancer and can be used to treat tumor metastases (p. 8, lines 7-16). These antibodies are cytotoxic with respect to cancer cells while simultaneously being relatively non-toxic to non-cancerous cells (p. 11, lines 16-20). The specification teaches that antibody H460-22-1 was produced by immunizing mice with primary lung cancer cultured cells and the NCI-H460 cell line (a human lung cancer cell line) and screening for cytotoxic activity and binding to normal and cancer cell lines, Example 5 and Table 5.

The specification teaches that H460-22-1 induced cell death in 21% of the NCI-H460 cells treated and induced cell death in only 5% of the CCD-12CoN

fibroblast cells, Table 5.

One cannot extrapolate the teaching of the specification to the scope of the claims because there is insufficient guidance and direction as to how to use an isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as Accession Number PTA-4622 because no antigen is defined and because the claims are drawn to humanized, chimerized, antibodies conjugated to cytotoxic moieties and read on an anticancer antibody as contemplated in the specification.

The specification teaches that the claimed antibody is useful for the treatment, prognosis, diagnosis, staging, and monitoring of cancer based on a screening assay that demonstrated that the claimed antibody preferentially killed cells from a lung cancer cell line, NCI-H460, compared to a fibroblast cell line in culture. However, although the antibody was produced by immunization with cells from a primary tumor and the lung cancer cell line, it cannot be predicted or determined from the information in the specification or in the art of record whether the claimed antibody is an anti-cancer antibody as defined and described by the specification. Further, it cannot be determined and cannot be predicted from the information in the specification whether the claimed antibody was produced in response to the primary lung cancer cells or from the lung cancer cell line. Certainly, the artifactual nature of cells in culture are well known in the art

and it cannot be determined whether the antigen to which the antibody binds is one that will be found on primary cancer cells or whether it is an artifact of the cell culture condition or whether the antigen against which the antibody was produced is in any way related to the *in vivo* cells from which the lung cell line was derived. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25,IDS) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. Drexler et al further teach that only a few cell lines contain cells that resemble the *in-vivo* cancer cells from which they were established and even for the bona fide cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207,IDS) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactual antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract,

p.764, IDS) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Thus, because the source of the antibody cannot be determined based on information in the specification, it cannot be determined whether the claimed antibody is in fact an anti-cancer antibody for any cancer that is found *in vivo*, especially in view of the fact that no primary cancer tissues or cells were used to determine the cytotoxicity of the antibody, nor was normal tissue or cells used as a control. Although the specification cites the CCD cell line as a "normal control", the fibroblast cell line is still a cultured cell line, subject to the same artifacts and peculiarities as other cell lines. Further, even if the claimed antibody binds to an antigen found on primary cancer cells, it cannot be determined from the information in the specification whether the antibody is an "anti-cancer" antibody as defined by the specification. In particular, it is well known in the art that there are many differences between cultured cells and their counterparts *in vivo*. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4, IDS) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions

characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro)*. Further, Dermer (Bio/Technology, 1994, 12:320 , IDS) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. The invention appears to be based on a cell culture system and based on the cell culture data presented in the specification, it

could not be predicted that, in the *in vivo* environment, that the claimed invention would function as an anti-cancer antibody. No evidence has been presented that the antigen to which the claimed invention binds is differentially expressed in cancer compared to normal controls *in vivo*. No evidence has been presented that the antigen to which the antibody binds would be diagnostic or prognostic for any cancer. No evidence has been presented that the antigen to which the claimed antibody binds is useful as a marker for staging or monitoring any cancer. No evidence has been presented that the claimed antibody would be effective as an anticancer therapeutic. The fact that antibody is cytotoxic in an *in vitro* system cannot be directly correlated to efficacy in an *in vivo* system. It is well known in the art that many of the factors known to limit human *in vivo* therapeutic efficacy of antibodies are lacking in *in vitro* model environments, for example, the *in vitro* system does not contain molecules that would be expected to proteolytically degrade the antibodies or that would activate an immunological response against the antibodies or that would nonspecifically absorb the antibodies in cells or tissues where the antibody has no effect. Further, it is clear that in the *in vitro* system exemplified, the antibodies are in contact with cells during the entire exposure period. This is not the case *in vivo*, where exposure to the target site may be delayed or inadequate to insure an adequate concentration of the

antibodies to be therapeutically effective. Those of skill in the art recognize that *in vitro* assays are useful to screen the effects of agents on cells. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared with the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a simple extrapolation of *in vitro* assays to human therapeutic efficacy with any reasonable degree of predictability.

Further, it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042, IDS) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of *in vivo* experimental evidence, no one skilled in the art would accept the assertion that the claimed antibody is an anti-cancer antibody useful for cancer treatment or therapy or any of the other contemplated uses. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65, IDS) teaches that tumors resist penetration by drugs

(p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39, IDS) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2).

It is clear that based on the state of the art, in the absence of *in vivo* experimental evidence, no one skilled in the art would accept the assertion that an isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as Accession Number PTA-4622 would function as anti-cancer antibody. In addition, Hartwell et al (Science, 1997, 278:1064-1068 IDS) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing

are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065). Again, no evidence has been presented that in the *in vivo* environment, the antigen to which the claimed antibody binds is differentially expressed on cancer as compared with normal cells. In addition, anti-tumor antibodies must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the cancer and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the antibody. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The antibody may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life of the antibody. In addition, the antibody may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where it has no effect, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no

working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to use the claimed invention with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to use the claimed invention.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the stare of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in

the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

The Examiner further states that:

If applicant were able to overcome the rejections set forth above Claims 27, 29-31, 33, and 34 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the isolated monoclonal antibody of claim 27, which is humanized, does not reasonably provide enablement for an isolated monoclonal antibody produced by the hybridomas deposited with the ATCC as Accession Number PTA-4622, which is chimerized, or antigen binding fragments thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broadly drawn to an isolated monoclonal antibody produced by the hybridomas deposited with the ATCC as Accession Number PTA-4622, which is chimerized, or antigen binding fragments

thereof. The monoclonal antibodies claimed include mouse monoclonal antibodies.

The specification teaches that the antibody produced by the hybridoma cell line (H460-22-1), deposited with the ATCC as Accession Number PTA-4622 as described in the preliminary amendment dated February 6, 2004, was produced by the immunization of mice with cells directly from a patient's lung cancer cells and with cells of the human lung large cell carcinoma cell line (NCI-H460), Example 5 and Table 5.

One cannot extrapolate the teachings of the specification to the scope of the claims because Winter et al (TIPS, 1993, 14:139-143) specifically teach that a major problem with the use of murine monoclonal antibodies in the treatment of human subjects is the development of human antimouse antibodies (HAMA) that can inactivate the injected antibodies. Thus, it would be expected that the injection of cross species antibody would result in anti-other species antibodies and/or cytotoxic T cells against the injected antibody. Further, Baselga et al (J. Clin. Oncol, 1996, 14:737-744) specifically teach that murine antibodies are limited clinically because they are immunogenic.

Given the above, it is clear that it is not possible to predict that an isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as Accession Number PTA-4622 would successfully treat a

human tumor in a human as contemplated in the specification. Thus it would require undue experimentation to practice the broadly claimed invention.

Responsive to the Examiner's comments, claim 27 has been amended to specifically set forth that the claim is directed towards "the" isolated monoclonal antibody produced from the hybridoma deposited as ATCC Accession Number PTA-4622; and claim 28 has been amended to specifically set forth that it is directed towards "a humanized antibody produced from the isolated monoclonal antibody of claim 27.

Real world utility for the PTA-4622 hybridoma cell line, and for the isolated monoclonal antibody produced by the hybridoma cell line identified as H460-22-1, and deposited with the ATCC as Accession Number PTA-4622, can be evidenced in S.N. 11/321,624, filed on Dec. 29, 2005. The '625 application evidences binding to CD-63 on a variety of cancer cells and cytotoxicity mediation of cells evidencing surface expression of CD63. See *inter alia* paragraphs 51-55, Figure 14, and Figures 24-29.

SUMMARY

In light of the foregoing remarks and amendment to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested. The Examiner is further requested to contact the undersigned to discuss the possibility of rejoinder of some of the withdrawn claims.

Respectfully submitted,

Ferris H. Lander

Ferris H. Lander
Registration # 43,377

McHale & Slavin, P.A.
2855 PGA Boulevard
Palm Beach Gardens, FL 33410
(561) 625-6575 (Voice)
(561) 625-6572 (Fax)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICANT	: David S. F. Young et al
INVENTION	: CANCEROUS DISEASE MODIFYING ANTIBODIES
SERIAL NUMBER	: 10/713,642
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EXAMINER	: Peter J. Reddig
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CORROBORATION FOR DEPOSITED MATERIALS

Mail Stop Non-Fee Amendment
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, David S.F. Young, a person in a position to corroborate the identity of Deposited Materials in U.S. Patent Application S.N. 10.713,642, filed on November 13, 2003, , do hereby state that the hybridoma cell line which was deposited in accordance with the Budapest Treaty, with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209 on September 4, 2002 under Accession No. PTA-4622 designated H460-22-1,is the same hybridoma cell line disclosed in the above-referenced patent application.

Respectfully submitted,

Date November 7, 2006

By _____

David S.F. Young
President and CSO
ARIUS Research, Inc.
55 York Street, 16th Floor
Toronto, Ontario M5J 1R7
Canada